REMARKS

Reconsideration of this application is respectfully requested.

Prior to entering the amendments above, the status of the claims is as follows. Claims 569-595, 597-643, 645-646, 648-651, 654-679, 681-682, 684-687, 690-714, 716-717, 719-747, 749-797, 800-803, 806-831, 833-834, 836-839, 842-866, 868-869, 871-899, 901-947, 949-950, 952-955, 958-983, 985-986, 988-991, 994-1018, 1020-1021, 1023-1051, 1053-1099, 1101-1102, 1104-1107, 1110-1135, 1137-1138, 1140-1143, 1146-1170, 1172-1173, 11751250, 1252-1253, 1255-1258, 1260-1294, 1296-1407, 1409-1568, 1570-1612 and 1614-1766 were previously pending in this application. Of these claims, the following claims have been allowed: claims 569-595, 597-599, 601-603, 625-633, 671-679, 684-687, 690-708, 719-722, 726-747, 753-755, 777-785, 823-831, 833-834, 836-839, 842-860, 871-899, 905-907, 929-937, 975-983, 985-986, 988-991, 994-1012, 1023-1026, 1030-1051, 1057-1058, 1082-1089, 1127-1135, 1137-1138, 1140-1143, 1146-1164, 1175-1176, 1247, 1700-1703, 1719-1722, 1729, 1742 and 1766.[1]

Applicants appreciate the indication in the March 12, 2002 Office Action (page 2) that rejections and/or objections not reiterated from previous office actions

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[1] **In the March 12, 2002 Office Action, the following claims were rejected: claims 600, 604-605, 608-611, 614-624, 643, 645-646, 648-651, 654-670, 681-682, 709-714, 716-717, 723-725, 752, 756-757, 760-763, 766-776, 768-797, 800-803, 806-822, 868, 869, 903-904, 908-909, 912-915, 918-928, 938-947, 949-950, 952-974, 1013-1018, 1020-1021, 1027, 1056, 1059-1061, 1064-1067, 1070-1081, 1090-1099, 1101-1102, 1104-1107, 1110-1126, 1165-1170, 1172-1173, 1177-1210, 1213-1229, 1232-1246, 1248-1250, 1252-1253, 1255-1258, 1260-1294, 1296-1407, 1409-1420, 1426, 1428, 1430, 1432, 1434-1459, 1462-1471, 1473-1488, 1491-1494, 1497-1568, 1570-1612, 1614-1699, 1704-1718, 1723-1728, 1730-1741, 1743-1744 and 1749-1765. In addition, objections were made to the following claims: 606-607, 612-613, 634-642, 749-751, 759, 764-765, 861-866, 901-902, 910-911, 916-917, 1028-1029, 1053-1055, 1125, 1211-1212, 1230-1231, 1421-1425, 1427, 1429, 1431, 1433, 1460-1461, 1472, 1489-1490, 1495-1496 and 1745-1748.**

have been withdrawn and that the two rejections in the latest Action constitute the complete set presently being applied against the present application.

Applicants' undersigned attorney also appreciates the courtesy and time extended to Dr. Dean L. Engelhardt, Senior Vice President for the Assignee's parent company, and him during the interview held on September 5, 2002.

I. Summary of Claim Amendments

In a sincere effort to define and clarify their claimed invention more clearly, Applicants have amended several of the claims above as follows. In claim 681, the dependency has been changed from "680" to -- 678 -- to reflect the fact that the former claim had been previously canceled. In each of claims 723, 749, 901, 909 and 1027, a claim has been deleted from the multiple dependent recitation. Thus, each of these five claims is no longer multiply dependent. These deletions were necessary in order to address the indefiniteness grounds (35 U.S.C. §112, second paragraph) raised in the March 12, 2002 Office Action, discussed *infra.*, this paper, pages 17-18. In claim 1025, the term "phosphate analog" has been inserted in order to provide a proper antecedent basis for later dependent claim 1059. Furthermore, claims 1744 and 1761 have each been amended to recite -- pyrimidine analogs -- instead of the previous "purine analogs" recitation. Again, this substitution is necessary in order to conform with the options later recited in both claims.

Claim 1411 has also been amended above for purposes of clarification. The first step of the three step detection process has been changed with the other two steps left unchanged. As now amended, the first step (A) of claim 1411 provides "(i) an oligo- or polynucleotide that is (1) complementary to and capable of specifically hybridizing to and forming a hybrid with a nucleic acid of interest or a

portion thereof and (2) capable of binding to or complexing with a non-radioactively detectable protein; and (ii) a non-radioactively detectable protein which has a binding affinity to a specific nucleic acid sequence." Support for the foregoing amendments to claim 1411 are found in the original specification. See Example XXXIV, pages 77-78, in the specification. The lac repressor is a classic example of a protein that binds to specific nucleic acid sequences, and it does not require any modification to the nucleic acid, e.g., a bound ligand, for its sequence-specific binding.

Applicants have also canceled claim 1260 above.

Finally, two new claims, 1767 and 1768, have been added. Claim 1767 is directed to a three step process for detecting non-radioactively labeled nucleic acid fragments with a sequencing gel. In the first step, detectable non-radioactively labeled nucleic acid fragments are provided or generated. Such fragments comprises one or more nucleotides or nucleotide analogs, which nucleotides or nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein the one or more nucleotides or nucleotide analogs comprise one or more fluorescent or chemiluminescent indicators on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof. In the second step of new claim 1767, the labeled fragments are subjected to a sequencing gel to separate or resolve said fragments. The third step calls for detecting non-radioactively each of the separated or resolved fragments by means of the fluorescent or chemiluminescent indicators.

Claim 1768 defines a process for resolving or separating non-radioactively labeled nucleic acids fragments with a sequencing gel. Again, three steps are recited in new claim 1768. In the first step, detectable non-radioactively labeled

nucleic acid fragments are provided or generated. These fragments comprise one or more nucleotides or nucleotide analogs that can be attached to or coupled to or incorporated into DNA or RNA, and wherein one or more fluorescent or chemiluminescent indicators are covalently attached, directly or through a linkage group, to at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog of said nucleotides or nucleotide analogs. In the second step of claim 1768, the labeled fragments are subjected to a sequencing gel to separate or resolve the fragments. In the third step, each of the separated or resolved fragments are detected non-radioactively by means of the fluorescent or chemiluminescent indicators attached to the one or more nucleotides or nucleotide analogs.

Support for the subject matter of new claims 1767 and 1768 is found in the specification. See, for example, the specification, page 84, second paragraph. See also, page 96, last paragraph, continuing through page 97, first paragraph.

As required under the new Simplified Amendment Practice. Replacement paragraphs/sections/claims to be used. 37 CFR 1.121, as set forth in the Changes to the Patent Rules (37 CFR 1.121 MPEP Bookmark, Volume 1, Issue 3), a marked-up version of the claims amended above is attached as Exhibit 1. This marked-up version is entitled "Version With Markings To Show Changes Made."

Entry of the above claim amendments and new claims is respectfully requested.

III. The Rejection Under 35 U.S.C. §112, First Paragraph (New Matter)

Claims 617-620, 622-623, 769-772, 774-775, 921-924, 926-927, 1073-1076, 1078-1079, 1224-1225, 1228-1229, 1235-1238, 1240-1241, 1341-1344, 1346-1347, 1436-1444, 1500-1503, 1505-1506, 1629-1630, 1633-1634, 1640-

1643 and 1645-1646 stand rejected for new matter under 35 U.S.C. §112, first paragraph. In the March 12, 2002 Office Action (pages 2-3), the Examiner stated:

> It is noted that the chemical linkages composed of a olefinic bond, various amines, etc. between the Sig moiety of the claims and the Base moiety of the labeled nucleotide was originally disclosed in original claims 77-82 only regarding Sig-Base attachment and not for Sig attachment to either the furanose or phosphate moieties therein. Instant claim 617-620, 622, 623, 769-772, 774, 775, 921-924, 926, 927, 1073-1076, 1078, 1079, 1224, 1225, 1228, 1229, 1235-1238, 1240, 1241, 1341-1344, 1346, 1347, 1436-1444, 1500-1503, 1505, 1506, 1629, 1630, 1633, 1634, 1640-1643, 1645 and 1646; now, however, cite such specific olefinic etc. attachment linkers to either the furanose or phosphate moieties of the labeled nucleotides of nucleotide analogs of the instant invention. These newly set forth specific linker species between furanose or phosphate moieties therefore add NEW MATTER to the instant disclosure.

The rejection for new matter is respectfully traversed.

That their claimed detectable non-radioactive Sig moiety can be attached by chemical linkages, including those chemical linkages comprising olefinic bonds, various amines and the like, to the various nucleotidyl elements, i.e., the base moiety, the sugar moiety and the phosphate moiety, is fully disclosed in Applicants' specification. In particular, on page 97, second paragraph, and continuing through page 98, first paragraph, Applicants disclose:

> As indicated in accordance with the practices of this invention, ***the Sig component could comprise any chemical moiety which is attachable either directly or through a chemical linkage or linker arm to the nucleotide, such as to the base B component therein, or the sugar S component therein, or the phosphoric acid P component thereof***.
>
> The Sig component of the nucleotides in accordance with this invention and the nucleotides and polynucleotides incorporating the nucleotides of this invention containing the Sig component are equivalent to and useful for the same purposes as the nucleotides

> described in the above-identified U.S. patent application Serial No. 255,223. More specifically, the chemical moiety A described in U.S. patent application Serial No. 255,223 is functionally the equivalent of the Sig component or chemical moiety of the special nucleotides of this invention. Accordingly, ***the Sig component or chemical moiety of nucleotides of this invention can be directly covalently attached to the P, S or B moieties or attached thereto via a chemical linkage or linker arm*** as described in U.S. patent application Ser. No. 255,223, as indicated by the dotted line connecting B and A of the nucleotides of U.S. Serial No. 255,223. The various linker arm or linkages identified in U.S. Ser. No. 255,223 are applicable to and useful in the preparation of the special nucleotides of this invention.
>
> [emphasis added]

In view of Applicants' original disclosure quoted above, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, are respectfully requested.

IV. The Rejection Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 600, 604, 605, 608-611, 614-624, 643, 645, 646, 648-651, 654-670, 709-714, 716, 717, 752, 756, 757, 760-763, 766-776, 786-797, 800-803, 806-822, 868, 869, 903, 904, 908, 909, 912-915, 918-928, 938-947, 949, 950, 952-974, 1013-1018, 1020, 1021, 1056, 1060, 1061, 1064-1067, 1070-1081, 1090-1099, 1101, 1102, 1104-1107, 1110-1126, 1165-1170, 1172, 1173, 1177-1210, 1213-1229, 1232-1246, 1248-1250, 1252, 1253, 1255-1258, 1260-1294, 1296-1329, 1332-1407, 1409, 1410, 1473-1488, 1491-1494, 1497-1568, 1570-1612, 1614-1616, 1619-1634, 1637-1699, 1704-1718, 1723-1728, 1730-1741, 1743 and 1749-1765 stand rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for being limited to furanose moieties as the SM structure in the instant claims, does not reasonably

provide enablement for the generic limitation given as "sugar". In the Office Action (pages 3-5), the Examiner stated:

> The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.
>
> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation necessary include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a suffcient amount for a *prima facie* case are discussed below.
>
> Reconsideration of the prosecution history has revealed that the previous amending of the claims to limit the SM or sugar moiety in the practice of the claimed non-radioactive nucleotide or nucleotide analog structures to furanose has been reamended back to "sugar" in amendment R, filed 5/23/00. Upon review of this amendment and supporting sugar structures revealed that only furanose sugar moieties are disclosed which form the structure in oligonucleotides or polynucleotides which will hybridize such as in hybridization probes with reasonable specificity and affinity. It is also noted that the early biochemical textbook of Lehninger summarized the hybridized structure of nucleic acids such as DNA on pages 638-639 as a specific structure which is needed in order to permit the hydrogen bonding to properly occur. It is noteworthy that even though this textbook is over 30 years the only notable hybridization probe backbone structure analog to be significantly utilized in biochemical reactions in that of peptide nucleic acids. These peptide nucleic acids, however, lack any sugar in the backbone, but rather utilize peptide bonds with spacing linkages and thus is not a nucleotide polymer. In

summary, the broad "sugar" wording for the SM moiety in the instant claims does not predictably support hybridization assay practice beyond the more limited form being "furanose".

The enablement rejection is respectfully traversed.

This matter was discussed at some length during the interview held on September 5, 2002. Applicants would like to reiterate that the structure of the sugar moiety in nucleic acid polymers is not altogether critical for hybridization purposes. In the case, for example, where the sugar moiety resides at the terminus of the polymer or even within the nucleic acid polymer, hybridization is still permitted and will occur. In the present specification, Applicants disclose three sugar moieties in the form of ribose, deoxyribose and dideoxyribose, each of which can be the terminal sugar moiety in the polynucleotide chain. The former two, ribose and deoxyribose, can reside anywhere in the polynucleotide chain. Dideoxyribose is a chain terminator and will be present at the terminus. In his classic textbook, DNA Replication [Second Edition, W. H. Freeman and Company, New York, 1992], Dr. Arthur Kornberg reviews a number of sugar analogs in Chapter 14 ("Inhibitors of Replication"). Sugar analogs which are chain terminators are listed at the top of Table 14-3 ("Nucleotide analogs incorporated into DNA or RNA") on page 447. As explained by Dr. Kornberg on page 446 under "14-3 Nucleotide Analogs Incorporated into DNA or RNA:"

> Certain analogs of the NTPs, modified in the sugar or base, are accepted by polymerases ***for pairing with the DNA template*** and are incorporated into nucleic acid, but subsequently block further chain growth or interfere with nucleic acid function. [emphasis added]

Most of these compounds were known in the art before the first filing of Applicants' application. A copy of pages 446-449 from Kornberg's DNA

Replication is attached as Exhibit 2. Please refer to footnotes 21-29 on pages 447-449.

Since hybridization is a property of the entire polynucleotide chain, the presence of one or more sites within the chain that may be occupied by analogs which are not furanoses, will not necessarily prevent hybridization of the nucleic acid strand to its complement. As alluded to in the Office Action, "spacing linkages" can compensate for the lack of sugar moieties altogether, as in the case of peptide nucleic acids cited by the Examiner.

In light of the foregoing remarks, reconsideration and withdrawal of the enablement rejection is respectfully requested.

V. The Rejection Under 35 U.S.C. §112, Second Paragraph (Definiteness)

Claims 681, 682, 723-725, 909, 1027, 1059, 1260, 1744 and 1761 stand rejected for indefiniteness under 35 U.S.C. §112, second paragraph. In the Office Action (pages 5-6), the Examiner stated:

> **[1]** Claim 681, 682, and 1260 depend directly or indirectly from a canceled claim.
>
> **[2]** Claim 909 is vague and indefinite because it cites "said sugar or sugar analog" whereas claim 873 from which it depends lacks any antecedent basis for said phrase. Clarification via clear claim wording is requested.
>
> **[3]** Claims 723 and 1027 are unclear due to the depending from a higher numbered claim.
>
> **[4]** Claim 1059 is vague and indefinite due to a lack of antecedent basis for "said . . . phosphate analog" due to no such analog being cited in claim 1025 from which claim 1059 depends.
>
> **[5]** Claims 1744 and 1761 are vague and indefinite in citing the selection of purine analogs wherein the options include pyrimidines. Clarification via clear claim wording is requested.

In order to ensure that each and every point in the indefininteness rejection above is addressed, Applicants' attorney has taken the liberty of inserting bold bracketed numbers before each point. The remarks below correspond to the bold bracketed numbers.

[1] The issue regarding the improper dependency of claims 681, 682 and 1260 has been obviated by amending claim 681 and deleting claim 1260. As indicated in the opening remarks to this paper, the dependency for claim 681 has been changed from formerly canceled claim 680 to claim 678. Claim 682 now depends properly from claim 681.

[2] As shown above, claim 909 has been amended so that it only depends from claim 904, and not from 873. The language in amended claim 909 regarding "said sugar moiety or sugar analog" is believed to be clear and definite, and possessing an antecedent basis in claim 904 from which it depends.

[3] As also shown above, claims 723 and 1027 have been amended by deleting claims from their prior multiple dependency recitation. In the case of claim 723, this claim now depends only from claim 722 (and not from the higher numbered 726). For claim 1027, this claim depends only from claim 1026 (and not from the higher numbered claim 1039).

[4] Claim 1025 has been amended by inserting the phrase "the phosphate analog." Thus, claim 1025 as amended now provides a proper antecedent basis for the language in claim 1059 regarding "said phosphate moiety or phosphate analog."

[5] Claims 1744 and 1761 have both been amended to properly recite "pyrimidine analogs" in place of the former language ("purine analogs").

In addition to the indefiniteness matters raised by the Examiner, Applicants have also amended claims 749 and 901 because of improper dependencies. In the

case of claim 749, this claim depended from claims 721 or 748, the latter a canceled claim. This improper dependency has been corrected by deleting "or claim 748" from the language in claim 749. With respect to claim 901, this claim also depended from previously canceled claim 900. That, too, has been corrected and claim 901 now only depends from claim 873.

In light of the foregoing amendments to the claims which obviate all the grounds for indefiniteness, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

VI. The Rejection Under 35 U.S.C. §102(b) (Anticipation)

Claims 1411-1420, 1426, 1428, 1445-1449, 1451, 1454, 1455, 1463-1471, 1712, 1714-1718, 1727, 1760 and 1761 stand rejected under 35 U.S.C. §102(e) as being clearly anticipated by Kourilsky et al., U.S. Patent No. 4,581,333, or alternatively, under 35 U.S.C. §102(b) as being clearly anticipated by Kourilsky et al., GB 2,019,408 A1. In the Office Action (pages 7-8), the Examiner stated:

> Kourilsky et al. discloses the preparation of an oligonucleotide or polynucleotide hybridization probe which has been modified with mercury in column 4, lines 2-6. A sample of DNA from blood (In column 6, lines 26-31, in vitro diagnosis via blood etc. samples is deemed to reasonably disclose samples from a living organism.) is then obtained and denatured in preparation for hybridization to the probe in column 4, lines 14-17. Then the probe is added to the sample under hybridization conditions followed by avidin/β-galactosidase addition as in column 4, lines 18-40. The avidin/β-galactosidase conjugate is capable of binding to or complexing with the non-radioactively detectable protein conjugate via biotin linked via cytochrome C bridges to the probe molecules. Non-hybridized probe reagent is separated (including by gel) followed by the detection of the probe DNA hybrids via the addition of a substrate for the enzyme, therein set forth as ONPG in column 4, lines 41-62. This method anticipates the above listed claims in that nonradioactive procedures are utilized throughout the method in the reference. It is also noted that the probe may be

directed to the detection of a variety of infections including bacteria etc. as listed in column 6, lines 18-46, as also required in certain instant claims. Genetic anomalies are also detectable as noted in column 6, lines 47-54, and required in instant claim 1426, for example. It is noted that the prior art of Kourilsky et al. (GB 2,019,408) disclosure, on pages 1-5 therein, of the above subject matter is equivalent to that of Kourilsky et al. (P/N 4,581,333). It is also noted that instant claim 1411 has been amended to remove any limitation as to why the non-radioactively detectable protein is capable of binding or complexing with the oligonucleotide or polynucleotide probe. This rejection was argued previously in the REMARKS of Amendment R, filed 5/23/00, but is non-persuasive to prevent this rejection due to the further claim amending as compared to the claims as worded on 5/23/00. Further consideration reveals that even the claim wording of 5/23/00 of claim 1411, for example, should not have prevented this rejection because the second segment of the probe which is recognized by vai a protein binding nucleic acid sequence does not contain any limitation as to what characteristics may bind such a protein. Thus, the modified probe of the references are deemed to containing protein binding sequence as previously worded in claim 1411 as well as the present claim wording wherein only some unlimited capability of protein binding or complexing is required to bind or complex a protein to the probe.

The anticipation rejection is respectfully traversed.

As noted above, Applicants have amended claim 1411 to recite that the non-radioactively detectable protein (ii) "**has a binding affinity to a specific nucleic acid sequence**." See Example XXXIV, pages 77-78 in the specification. Unlike Applicants' claimed invention as set forth in amended claim 1411, neither of the cited Kourilsky documents disclose a protein which "has a binding affinity to a specific nucleic acid sequence." The use of Applicants' sequence-specific protein to detect nucleic acids is a patentable material element altogether lacking in the Kourilsky disclosures. The latter disclose proteins which bind to a ligand which are attached and present on the nucleic acid. The present invention embodied in claim

1411 requires no modification to the oligo- or polynucleotide (i). Only the presence of specific nucleic acid sequences which form recognition elements for the cognate protein (ii) is necessary for protein binding.

In view of the lack of material identity between the cited Kourilsky disclosures and the claimed invention at hand, Applicants respectfully request reconsideration and withdrawal of the anticipation rejection.

Before addressing the next issue, Applicants would like to bring U.S. Patent No. 6,221,581 B1 to the attention of the Patent Office and the Examiner. This patent issued on April 24, 2001 and is assigned to the instant Assignee. A copy of U.S. Patent No. 6,221,581 B1 is attached as Exhibit 3.

VII. The Rejection Under 35 U.S.C. §103(a) (Obviousness)

Claims 1411-1417, 1419, 1428, 1430, 1432, 1434, 1435, 1440, 1441, 1444-1459, 1462-1471, 1712, 1714-1718, 1727, 1760 and 1761 stand rejected under 35 U.S.C. §103(a) as being unpatentable over either of Langer et al. [PNAS 78:6633 (1981)] or Dale et al. [Biochemistry 14:2458 (1975)]. In the Office Action (pages 9-11), the Examiner stated:

> On pages 6633-6637 the Langer et al. reference describes the synthesis and various characteristics of biotin-labeled polynucleotides and sets forth a reasonable expectation of success for the usage of such polynucleotides as probes in hybridization assays for target nucleic acids. The motivation and suggestion to actually perform such assays is supplied in the DISCUSSION section on page 6637, last 4 line of the lefthand column through line 11 of the righthand column. In this same DISCUSSION section the motivation and suggestion to utilize non-radioactive protein which binds to the biotin-labeled probe is also set forth. Such non-radioactive proteins are listed as fluorescein labeled goat IgG with antibiotin antibody or antibody-phosphatase conjugates which bind or complex with probes during the assay for detection. Such IgG or antibodies are also well known to be glycosylated and therefore include a polysaccharide or monosaccharide

therein. The biotin-probe with non-radioactive protein detection complex formation and detection thereof is deemed an embodiment of instant claims 1411 etc. It is noted as discussed above that instant claim 1411 does not limit the binding of complex formation mechanism between the probe and protein of the claim in any specific way so as to prevent this rejection. It is also noted that the target nucleic acids utilized in the reference are directed to the bacterial microorganism E. coli which is a target type required in certain instant claims. In said DISCUSSION section the suggestion of utilizing tissue sections is also set forth which motivates, therefore eukaryotic organisms as these are deemed to be the only organism type with tissue, which are also generally obtained from living organisms.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the suggested and motivated hybridization assay as given in the reference to practice the instant invention with a reasonable expectation of success due to the various characterization experiments in the reference to document the usability of the biotin-labeled probes therein in various types of hybridization assay. Similarly, the Dale et al. reference describes the hybridization characteristics of mercurated probes and motivates and suggests their use in hybridization assays in the last sentence of the abstract therein.

The obviousness rejection is respectfully traversed.

In response to the Langer rejection, Applicants respectfully submit that their claimed invention, as set forth in independent claims 1411 and 1712, is neither suggested nor disclosed by the cited publication. First, with respect to the invention embodied by claim 1411, Applicants point out Langer et al. disclose analogs of dUTP and UTP containing a biotin molecule covalently bound to the C-5 position of the pyrmidine ring through an allylamine linker arm. Nowhere in Langer's disclosure is there any mention or suggestion for detecting nucleic acids with a protein having a nucleic acid sequence-specific binding affinity, as set forth in claim 1411. Furthermore, Langer et al. do not disclose or suggest the use of a

gel to separate or resolve nucleic acid hybrids which have been formed in liquid phase, as set forth in claim 1712.

With respect to Dale et al., again, there is no mention or suggestion for detecting nucleic acids with a protein having a nucleic acid sequence-specific binding affinity, as set forth in Applicants' claim 1411. Dale et al. relies upon modified nucleotides. Furthermore, Dale et al. do not disclose or suggest the use of a gel to separate or resolve nucleic acid hybrids which have been formed in liquid phase, as defined in claim 1712.

In view of the above amendments to the claims and the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the first obviousness rejection.

VIII. The Rejection Under 35 U.S.C. §103(a) (Obviousness)

Claims 1298-1305, 1315, 1318, 1320, 1324-1333, 1335-1340, 1345-1352, 1358, 1359, 1371, 1373, 1379, 1385-1390, 1399-1401, 1403, 1404, 1406, 1407, 1409, 1582, 1583, 1585-1591, 1593-1597, 1599, 1601, 1605-1609, 1611, 1612, 1614-1618, 1620-1639, 1644-1650, 1656, 1657, 1669, 1671, 1677, 1678, 1684-1688, 1695-1699, 1705, 1708, 1709, 1711, 1725, 1726, 1730, 1749-1751, and 1758-1761 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Hartman et al. (Biopolymers 20:2635 (1981)]. In the Office Action (pages 11-12), the Examiner stated:

> Hartman et al. suggests and motivates the use of methacrylate modified azoRNA in hybridization assays in the title and abstract. The abstract and analysis of said modified azoRNA as hybridization probes. The hybridization of probe to known chromosomal targets is described on page 2636, first paragraph, which is deemed a type of karyotyping. On page 2641, a non-radioactive label structure at the C-4 position of cytidine is shown. These probes are made by the incorporation of semicarbazide-modified nucleotides as outlines on

page 2639 which is additionally modified by the methacrylate in the reference. A reasonable expectation of success in using such a probe in hybridization assays include its measurement at 248 nanometers of UV absorption is shown on page 2644 in Figure 5 and elaborated in more detail in the DISCUSSION section on pages 2645-2647. These labels also include the binding or chelation of heavy metal atoms for detection as discussed on page 2637, lines 1-13, as also embodiments of certain instant claims. The use of these probes is also motivated by an increase in sensitivity as discussed in the bridging paragraph between pages 2636 and 2637 wherein radioactive or fluorescent detection methods are suggested to be replaced by the polymerization of methacrylate polymer at hybridization sites which binds markers.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the methacrylate polymerization type of hybridization assay with non-radioactive ribonucleotide probes as given in the reference to result in embodiments of the instant invention.

The second obviousness rejection is respectfully traversed.

It is respectfully submitted that a person of ordinary skill in the art would not have been motivated to use Hartman's disclosed azo RNA as a nucleic acid probe because the authors themselves disclose on page 2645 (under "DISCUSSION") that "one initiator can cause the linking of many methacrylate monomer units,[16]," thus, signal generation can just as well result from small quantities of unbound probe being present in the absent of any hybridized target.

With respect to Hartman's UV absorption measurements disclosed on page 2644, Figure 5, Applicants respectfully point out that the authors use this information to actually show the inability of azo RNA to hybridize to complementary sequences. In particular, Hartman et al. disclose in the first full paragraph on page 2644:

> Mixing buffered saline solutions of poly(u^4C) and poly(I) in different ratios resulted in no detectable hypochromicity, as shown in Fig. 5 (open circles). Since

poly(C) and poly(I) combine to form a double helix with concomitant hypochromicity (see Fig. 5, solid circles), it appears that poly(u^4C) does not form a double helix with poly(I) under these conditions.

The measurement at 248 nanometers, as disclosed by Hartman et al., is only appropriate for measuring the binding of unlabeled probes to complementary sequences, without significant contribution of any signal from the poly(u^4C) tail. Accordingly, a person of ordinary skill in the art would not have been motivated to use Hartman's disclosed azo RNA in a nucleic acid detection assay, because the absence of any target might not be distinguishable from the presence of target. This could result in the generation of false positive signals.

In view of the foregoing remarks, reconsideration and withdrawal of the second obviousness rejection is respectfully requested.

VI. Previous Submission of Art-Related Documents

Applicants acknowledge the Examiner's remarks in the March 12, 2002 Office Action (pages 12-13) concerning their October 9, 2001 Communication To Transmit Documents Cited In Applicants' 4th Supplemental Information Disclosure Statement. English translations have been ordered for the following five (5) previously submitted German and Japanese language documents:

Kagakukai ed., "Fluorescence tagging" Biochemistry Experiments Course 2, Nucleic Acid Chemistry III, pages 299-317 (1977) **[Exhibit 53 to September 19, 2001 4th Supplemental IDS]**;

Douglass et al., "Methods and instrumentation for fluorescence quantitation of proteins and DNA's in electrophoresis gels at the l ng level," Electrophoresis '78 N. Catsimpoolas, ed., pages 155-165 (1978) **[Exhibit 59 to September 19, 2001 4th Supplemental IDS]**;

Gilbert W., "DNA-sequenzierung und gon-struktur (Nobel-Vortrag)" Angenwandte Chemie 93:1037-1046 (I981) **[Exhibit 60 to 9/19/01 4th Supplemental IDS]**;

Husimi, Y. "DNA Sequences," Oyo Buturi 51(12):1400 (I982) **[Exhibit 68 to 9/19/01 4th Supplemental IDS]**; and

Ulanov et al., "Electron microscopic determination of guanosine localization in DNA," Chem. Abst. 67:1692 (I967) (abstract no. 17910c) **[Exhibit 72 to 9/19/01 4th Supplemental IDS]**.

As soon as the English translations for the above-listed documents are received, Applicants' attorney will submit them to the U.S. Patent Office for consideration by the Examiner.

Regarding other art-related documents, Applicants are filing their Sixth Information Disclosure concurrently with the filing of this paper. In their Sixth IDS, the following documents in the form of English translations are being submitted:

1. Japanese Patent Application No. S59-44648, Applicant: Mimata Seisakusho Co., Ltd.; Inventor: Takashi Satoh; Filed: September 7, 1982; Published: March 13, 1984 [**Exhibit 1** herewith] (formerly Exhibit 30 in September 19, 2001 Fourth Information Disclosure Statement);

2. Japanese Patent Application No. S59-93100; Applicant: Wakunaga Industries Co., Ltd.; Inventor: Ryo Fuwa; Filed: August 9, 1982; Published: May 29, 1984 [**Exhibit 2**] (formerly Exhibit 31 in September 19, 2001 4th IDS);

3. Japanese Patent Application No. S59-126252; Applicant: Fuji Photo Film Co., Ltd.; Inventor: Hisashi Shiraishi; Filed: January 8, 1983; Published: July 20, 1984 [**Exhibit 3**] (formerly Exhibit 32 in September 19, 2001 4th IDS);

4. Japanese Patent Application No. S60-161559; Applicant: Hitachi Ltd.; Inventor: Hideki Kamihara et al.; Filed: February 1, 1984; Published: August 23, 1985 [**Exhibit 4**] (formerly Exhibit 33 in September 19, 2001 4th IDS);

5. Japanese Patent Application No. S60-242368; Applicant: Hitachi Ltd.; Inventor: Yoshinori Harada et al.; Filed: May 16, 1984; Published: December 2, 1985 [**Exhibit 5**] (formerly Exhibit 34 in September 19, 2001 4th IDS);

6. Japanese Patent Application No. S49-126395; Applicant: Toshio Maeda, President, Kyoto University; Inventor: Masanobu Tokushige; Filed: April 4, 1973; Published: March 12, 1974 [**Exhibit 6**] (formerly Exhibit 44 in September 19, 2001 4th IDS); and

7. Japanese Patent Application No. S58-502205; Applicant: Pasteur Institute; Inventor: Kourilsky et al.; Filed: December 29, 1982; Published: December 22, 1983 [**Exhibit 7**] (formerly Exhibit 46 in September 19, 2001 4th IDS).

Copies of the 7 above-listed documents are being submitted as Exhibits 1-7 to Applicants' concurrently filed Sixth IDS. A completed Form PTO-1449 is also attached as Exhibit 8. As indicated in the Sixth IDS, these English translations were prepared in response to the Examiner's remarks on page 3 in the previous October 9, 2001 Office Action

Favorable action is respectfully sought.

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SUMMARY AND CONCLUSIONS

Claims 569-595, 597-643, 645-646, 648-651, 654-679, 681-682, 684-687, 690-714, 716-717, 719-747, 749-797, 800-803, 805-831, 833-834, 836-839, 842-866, 868-869, 871-899, 901-947, 949-950, 952-955, 958-983, 985-986, 988-991, 994-1018, 1020-1021, 1023-1051, 1053-1099, 1101-1102, 1104-1107, 1110-1135, 1137-1138, 1140-1143, 1146-1173, 1175-1250, 1252-1253, 1255-1258, 1260-1294, 1296-1407, 1409-1568, 1570-1612 and 1614-1748 are being presented for further prosecution on the merits. Claims 681, 723, 749, 901, 909, 1025, 1027, 1411, 1744 and 1761 have been amended. Claims 1767 and 1768 have been added. Claim 1260 has been canceled.

The fee for adding new claims 1767 and 1768 is $18, based upon the presentation of one additional claim due to the cancellation of one claim. The Patent and Trademark Office is hereby authorized to charge the requisite $18 claim fee to Deposit Account 05-1135. No other fee or claim fee is believed due in connection with this filing. In the event that any other fee or fees are due, however, The Patent and Trademark Office is hereby authorized to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be

contacted at the number provided below.

Respectfully submitted,

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MARKED-UP VERSION OF AMENDED CLAIMS

681. (Amended) The process according to claim [~~680~~] **678**, wherein A comprises a magnetic component.

723. (Amended) The process according to [~~claims~~] **claim** 722 [~~or 726~~], wherein said organism is selected from the group consisting of bacteria, fungi, viruses, yeast, mammals, and a combination of any of the foregoing.

749. (Amended) The process according to claim 721 [~~or 748~~], wherein said incorporation is carried out by means of a polymerizing enzyme.

901. (Amended) The process according to claim 873 [~~or 900~~], wherein said incorporation is carried out by means of a polymerizing enzyme.

909. (Amended) The process according to [~~claims~~] **claim** [~~873 or~~] 904, wherein said sugar moiety or sugar analog comprises a monosaccharide.

1025. (Three Times Amended) A process for determining the sequence of a nucleic acid of interest, comprising the step of detecting non-radioactively with a sequencing gel one or more detectable non-radioactive labeled nucleic acid fragments comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified on at least one of the sugar moiety, the sugar analog, the phosphate moiety, **the phosphate analog,** the base moiety or the base analog thereof.

1027. (Twice Amended) The process according to [~~claims~~] **claim** 1026 [~~or 1030~~], wherein said organism is selected from the group consisting of bacteria, fungi, viruses, yeast, mammals, and a combination of any of the foregoing.

1411. (Three Times Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

(A) providing:

(i) an oligo- or polynucleotide **that is (1)** complementary to and capable of [~~(1)~~] specifically hybridizing to and forming a hybrid with a nucleic acid of interest or a portion thereof and (2) capable of binding to or complexing with a non-radioactively detectable protein; and

(ii) a non-radioactively detectable protein which **has a binding affinity to a specific nucleic acid sequence** [~~is capable of binding to or complexing with said nucleic acid hybrid~~] ;

(B) contacting a sample suspected of containing said nucleic acid of interest with said oligo- or polynucleotide (i) and said non-radioactively detectable protein (ii) to form a complex; and

(C) detecting non-radioactively the presence of said non-radioactively detectable protein in said complex to detect said nucleic acid of interest.

1744. (Amended) The process of claim 1743, wherein said [~~purine~~] **pyrimidine** analogs are selected from the group consisting of thymidine analogs, uridine analogs, deoxyuridine analogs, cytidine analogs and deoxycytidine analogs.

1761. (Amended) The process of claim 1760, wherein said [~~purine~~] **pyrimidine** analogs are selected from the group consisting of thymidine analogs, uridine analogs, deoxyuridine analogs, cytidine analogs and deoxycytidine analogs.

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